II. REMARKS

Preliminary Remarks

A. Declaration

The examiner has objected to the declaration as failing to adequately identify the specification to which the declaration is directed, and cites M.P.E.P. § 602. The examiner acknowledges that the declaration identifies the specification, but objects because it does not identify the case no. or filing date of the originally filed application.

The applicants respectfully submit that the declaration is proper. For the requirements of an oath or declaration, M.P.E.P. § 602 refers to 37 C.F.R. § 1.63. Under 37 C.F.R. § 1.63(b)(1), a declaration must identify the application to which it is directed; however, there is no requirement that the declaration identify a U.S. application by application number and filing date. In the present case, the declaration clearly identifies the application to which it is directed by identifying the title of the application and the names and addresses of the inventors. The declaration submitted in this divisional application is a copy of the declaration that was submitted with the original application papers of the parent application, U.S. Patent Application No. 09/525,007, filed March 14, 2000. Since an application number and filing date had not been assigned at the time the declaration was executed, they could not have been identified in the document. 37 C.F.R. § 1.63(d)(1) states that a newly executed oath or declaration is not required in a continuation or divisional application when the previous declaration was proper and a copy of that declaration is submitted. Those circumstances apply in the present case. Accordingly, withdrawal of the objection to the declaration is respectfully requested.

B. Priority

The examiner has objected to the priority claim set forth in this application, stating that a foreign priority claim must be timely made in this application. The applicants have timely claimed priority by submitting a preliminary amendment on September 29, 2003, which amended the first page of the application to claim priority to both the parent U.S. application and the foreign application. An Application Data Sheet was filed on the same day making the same priority claim. A certified copy of the foreign application for which priority benefit is claimed was filed with the parent application, U.S. Patent Application No. 09/525,007, which issued as

U.S. Patent No. 6,627,609, on September 30, 2003. The applicants therefore submit that a timely and proper priority claim has been made, and respectfully request that the objection be withdrawn and the priority claim be acknowledged.

C. Amendment of the Specification

The examiner has objected to the specification on page 2, line 26 as failing to include a sequence identifier. In response, the paragraph beginning on page 2, line 23, is amended to include the SEQ ID NO in parentheses following the peptide sequence on page 2, line 26. Withdrawal of the objection is therefore respectfully requested.

D. Amendment of the Claims

Claims 19-22 are pending.

Claims 19, 21, and 22 are amended by replacing a semi-colon with a comma.

Claim 21 is further amended to specify "prostate carcinoma" rather than "prostate cancer," as described on page 7, line 10.

Patentability Remarks

A. Objections to the Claims

The examiner has objected to claims 19-22 because the applicants use both a comma and a semicolon in the recited definition of substituent Xxx^6. While the applicants believe that the claims are clear on their face with the inclusion of both commas and semicolons, the objected-to semicolons in claims 19, 21, and 22 have been replaced with commas. In view of this amendment, the applicants respectfully request that this objection be withdrawn.

B. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 21-22 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable one of skill in the art to use the claimed invention without undue experimentation.

Basis for rejection

Claim 21 is directed to a method of treating prostate carcinoma or breast cancer by administering a peptide LHRH antagonist. Claim 22 is similarly directed to a method in which a peptide LHRH antagonist is administered to a patient to treat benign prostate hyperplasia (BPH) or endometriosis. The examiner alleges that since the claims encompass treating any stage or form of prostate cancer or breast cancer, and since one cannot reliably predict from *in vitro* results if a cancer treatment will be effective *in vivo*, undue experimentation would be required to make or use the claimed invention. In support of the rejection, the examiner refers to the factors identified in Ex parte Forman, 230 USPQ 546 (BPAI 1986) that are to be considered in determining if an application complies with the enablement requirement of 35 U.S.C. § 112, first paragraph (*see* pages 3-5 of the official action). Regarding (1) the nature of the invention, the examiner notes that the claimed invention is a method of treating prostate and breast cancer, benign prostate hyperplasia, and endometriosis. Regarding (2) the state of the art, and (3) the predictability of the art, the examiner alleges that "*in vitro* testing for cancer therapies/treatments is unpredictable when assuming *in vitro* results automatically extrapolate to *in vivo* applicability," and cites an article by Dermer ("Another Anniversary for the War on Cancer", 1994). Regarding (5) the breadth of the claims, the examiner notes that claim 21, directed to a "method of treating prostate cancer or breast cancer," includes treatment of "many varying patient groups and subgroups with regards to cancer type and treatment levels." In regard to (6) the amount of guidance presented, and (7) the presence or absence of working examples, the examiner alleges that "the specification is lacking in even minimum guidance or working examples that would be suggestive of *in vivo* efficacy regarding the claimed methods of use." Regarding (8) the quantity of experimentation necessary, the examiner concludes that "[s]ince cancer treatments are unpredictable regarding the extrapolation from *in vitro* to *in vivo* uses and efficacy, and due to the absence of guidance or working examples teaching toward predictability and efficacy, the quantity of experimentation necessary to make and/or use the claimed methods and compounds of the methods necessary for use of the invention would be an undue burden on one of skill in the art."

The enablement requirement of 35 U.S.C. § 112, First Paragraph, is met

The applicants respectfully submit that in view of the nature of the invention, the state and predictability of the art at the time of filing, the level of skill and knowledge of persons in working in the field of the invention, the scope of the claims, and the disclosed experimental data; *i.e.*, the same factors identified in Ex parte Forman to which the examiner refers, one of skill in the art would have no difficulty following the teachings of the specification and successfully practicing the claimed therapeutic methods without having to perform undue experimentation.

Claim 21 is directed to a method of treating prostate carcinoma or breast cancer by administering a peptide LHRH antagonist. Claim 22 is similarly directed to a method in which a peptide LHRH antagonist is administered to a patient to treat benign prostate hyperplasia (BPH) or endometriosis. The application reviews the state of the art at the time of filing to teach that the peptide LHRH antagonists of the claimed invention are analogs of peptide LHRH antagonists that were recognized at the time of filing as having therapeutic efficacy (*see* page 1, lines 4-11, and page 2, lines 23-38). The application describes *in vitro* assay methods for quantitatively determining the binding affinities (K_D) of peptide LHRH antagonists to cellular LHRH receptors, and their functional activities (IC_{50}), and shows that peptide LHRH antagonists of the claimed invention bind to cellular LHRH receptor with affinities and functional activities comparable to those of cetrorelix, a peptide LHRH antagonist with known therapeutic efficacy (*see* Example 9 (pages 19-23).

The examiner has cited Dermer (1994) as teaching that the efficacy of a cancer therapy cannot be predicted from the results of *in vitro* testing, and has cited In re Marzocchi, 169 USPQ 367 (CCPA 1971), as holding that a rejection for failure to teach how to make and/or use is proper "where a statement is, on its face, contrary to generally accepted scientific principles." *See* page 3 of the official action. Dermer teaches that immortalized cancer cell lines that are used in cancer research are metabolically different from real cancer cells found in a patient with cancer. According to Dermer, "only differentiated, aging cells in organs are susceptible to cancer," and experimental data for "undifferentiated, ageless 'normal' cell lines – like 3T3 in which the pathways that are struck by cancer, like those of development and aging, are absent – cannot be relevant to cancer initiation in humans." Dermer considers the "continued

ineffectiveness" of chemotherapy against cancer to be due to the disparate character of the human tumor cell lines that are used to screen agents for chemotherapeutic activity. Dermer also considers studies of immunotherapy against tumors grown from cell lines to be flawed because the immunogenicity of such tumors is different from that of natural tumors. Dermer calls for additional research to identify models that mimic the human body and normal and malignant biochemical pathways of human cells. *See* paragraphs 3-8.

Dermer's concerns that experimental results obtained using cancer cell lines fail to predict the efficacy of chemotherapeutic agents and cancer immunotherapies *in vivo* are not relevant to the claimed invention of the present application. As discussed above, at the time the priority application was filed persons of skill in the art recognized that peptide LHRH antagonists were effective therapeutic agents for the treatment of hormone-dependent tumors such as prostate carcinoma and breast cancer, and hormone-influenced non-malignant disorders such as BPH and endometriosis. The *in vitro* assays described in the present application use cultured mammalian cells that express human LHRH receptor, and reliably determine the binding affinity (K_D) with which a peptide LHRH antagonist binds to the human LHRH receptor (*see* method 1, pages 20-21), and the functional ability of a peptide LHRH antagonist to antagonize LHRH activity in the presence of a potent LHRH agonist (*see* method 2, pages 21-22). Persons of skill in the art at the time of filing reasonably considered the results of *in vitro* assays such as those described in the present application, in which the binding affinities (K_D) for LHRH and the functional activities (IC_{50}) of peptide LHRH antagonists are determined relative to those of a peptide LHRH antagonist of known therapeutic activity, to be predictive of therapeutic effect *in vivo*.

As described in the application, and discussed above, persons of skill in the art at the time of filing were familiar with and practiced methods in which therapeutic peptide LHRH antagonists are administered to effectively treat prostate carcinoma, breast cancer, BPH and endometriosis. The techniques used in the known and effective treatments can be applied when using the LHRH antagonists disclosed in this application. The examiner has acknowledged that the skill of those in the arts related to the claimed invention is high (*see* page 4 of the official action, with regard to factor (4)). In fact, such persons of skill in the art typically have an M.D. degree and/or a Ph.D. degree, and a high level of knowledge of fields related to the invention

such as oncology and endocrinology. Such persons of skill in the art would be able to follow the teachings of the application to successfully prepare peptide LHRH antagonists of the claimed invention, and use them for successful treatment of prostate carcinoma, breast cancer, benign prostate hyperplasia and endometriosis. Such persons of skill in the art would be able to determine effective dosages of the claimed LHRH antagonists through routine experimentation, and would administer the claimed LHRH antagonists using protocols based on those known to be effective for treating said diseases and disorders at the time of filing.

With regard to factor (5), the breadth of the claims, the examiner has pointed out that claim 21, directed to a "method of treating prostate cancer or breast cancer," includes treatment of "many varying patient groups and subgroups with regards to cancer type and treatment levels." Claim 21 is amended to specify treatment of prostate carcinoma or breast cancer, I accord with the description of the invention on page 7, line 10. The applicants submit that variability in the responsiveness of individual patients to the claimed methods does not prevent one of skill in the art from being able to predict that the claimed methods operate effectively to provide therapeutic benefit, or from being able to practice the claimed methods with therapeutic efficacy. At the time the priority application was filed, persons of skill in the art of cancer treatment recognized that individual cancers of any given cancer classification or type (*e.g.*, prostate carcinoma or breast cancer) have unique molecular and cellular characteristics that may increase or decrease the response of the cancer to therapy, and that the response of any cancer to a particular therapeutic agent cannot be reliably predicted. However, persons of skill in the art also recognized that the efficacy of an anti-cancer agent against a cancer of a specific type can be described in terms of the probability that the agent will have anti-cancer activity against the cancer type in question (*i.e.*, the percentage of patients expected to respond). For example, colon cancer is relatively resistant to anti-cancer agents, and the probability that a patient with colon cancer will respond to an anti-cancer agent is usually considered to be relatively low; whereas the probability that a patient with a different type of cancer will respond to an anti-cancer may be significantly greater. In the case of the presently claimed invention, it was recognized at the time of filing that there is a high probability that patients with hormone-dependent diseases and disorders such as prostate carcinoma, breast cancer, benign prostate hyperplasia and

endometriosis will receive therapeutic benefit from administration of peptide LHRH antagonists, *e.g.*, cetrorelix.

The applicants strongly traverse the examiner's allegation, in the quotation from In re Marzocchi, that the teachings of the application regarding making and using the peptide analogs and methods of the claimed invention to effectively treat prostate carcinoma, breast cancer, BPH, and endometriosis are on their face, "contrary to generally accepted scientific principles." (*see* page 3 of the official action). The court in In re Marzocchi stated:

> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

See id., (CCPA, 1971), cited in In re Brana, 34 USPQ2d 1437-1444 (Fed. Cir. 1995).

As discussed above, the reasons given by the examiner for considering the claimed invention to be unpredictable and requiring undue experimentation are not applicable or relevant to the invention described and claimed by the present application. As described in the application and as discussed above, one of skill in the art would understand that the claimed methods would operate successfully to provide effective treatment of prostate carcinoma, breast cancer, BPH and endometriosis, in view of the experimental data showing that binding affinities (K_D) for LHRH receptor and functional activities (IC_{50}) of peptide LHRH antagonists of the claimed invention are comparable to those of a peptide LHRH antagonist that has high therapeutic efficacy *in vivo*. Moreover, any experimentation required to practice the claimed invention successfully would be of routine order, pertaining to determining optimal dosage and administration regimen.

For the reasons discussed above, the applicants submit that in consideration of the factors set forth in Ex parte Forman (BPAI, 1986), the application satisfies the requirement of 35 U.S.C. Section 112, first paragraph, for enablement. The examiner has not provided substantiated reason to doubt the objective truth of the statements in the application describing how to make and use the claimed invention without having to perform undue experimentation. Accordingly,

withdrawal of the rejection of claims 21 and 22 under 35 U.S.C. § 112, first paragraph, for lack of enablement, is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: June 30, 2006

By 

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